II. REMARKS

Claims 1-33 were originally pending in this application. New Claim 34 and Claim 35 are added herein and Claim 6 and Claim 9 are cancelled herein. Accordingly, Claims 1 –5, 7, and 9 –35 are presently pending in the above-identified application. Examiner's Office Action Summary (Form PTO-326) dated 08/22/2002 indicates that Claims 1 – 22 are pending in the above-identified application. It is believed that this is an inadvertent error as Examiner indicates on page 2 of the Official Action that Claims 16 – 33 are allowable. Examiner further states that Claims 7 – 9 would be allowable if written in independent form. New independent Claims 34 and 35 are added herein incorporating respectively the subject matter of Claim 1 and Claim 6 and Claim 1 and Claim 8. Old Claims 6 and 8 are cancelled herein. Claim 7 is amended to depend from New Claim 34 and Claim 9 is amended to depend from New Claim 35. It is respectfully asserted that Claims 34, 35, 7, 9, and Claims 16 – 33 describe allowable subject matter.

III. The Rejections

A. Rejections Under 35 USC §102(b).

Claims 1, 5 and 6 are rejected under 35 USC 102(b) as being anticipated by US Pat. No. 4,851,211 9 (Adjei et al.) Examiner contends that Adjei teaches the following:

> [A]n aerosol formulation comprising organic solvent (ethanol), a luteinizing hormone (protein) suspended in ethanol, and lipophilic counterion (derivatized carbohydrate).

Contrary to Examiner's assertion, Adjei does not disclose a stable suspension of a biologically active protein in ethanol. What Adjei does disclose is an aerosol formulation required to contain the following components:

Active Drug Substance	LHRH Analog
Lipophilic counterion	Alkyl ($C_5 - C_{12}$) sulfonic acid or salts thereof
Carrier Liquid	Mixture of water and EtOH
Propellant	Chlorofluorocarbon

The formulations taught by Adjei are required to contain a $C_5 - C_{12}$ sulfonic acid/or salts as a "lipophilic counterion". The term "lipophilic counterion" refers to organic acids or their salts with a pka sufficiently low to render them ionizable at the product pH and includes but is not limited to alkyl ($C_5 - C_{12}$) sulfonic acids and salts thereof, palmitates, dioctylsulfosuccinate and its congeners, stearates and salicylates. Adjei discusses the problems associated with prior art LHRH analogs at col. 1, lines 37-52 and teaches that:

> LHRH analogs are practically insoluble in fluorocarbons. In mixtures of ethyl alcohol and fluorocarbons, the solubility of leuprolide approaches 3 mg/ml, which is not satisfactory due to dose requirements. This solubility estimate is not significantly affected by the presence of nonionic surfactants because, in part, of solubility and dielectric limitations of such surfactants. In mixtures of fluorocarbons, ethyl alcohol and water, experimental results showed equilibrium solubility of leuprolide to approach 5 mg/ml which is still unacceptable. At high concentrations of ethyl alcohol, a gel-like mass forms resulting in a colloidal dispersion that does not clear at room temperature for up to one month. At water concentrations of 10% or greater, a complete phase separation occurs making a homogeneous formulation impractical and renders aerosolization impractical.

The above described prior art problems are overcome by the inclusion of a lipophilic counterion in the formulations of Adjei, which increases the solubility of LHRH in the formulation (col.5, lines 19-27).

The aerosol formulations of Adjei are required to contain a propellant. The formulation is designed to be filled into an aerosol canister under pressure such as a metered dose inhaler (MDI). Such aerosol canisters are well known in the art. See US 6,261,539, col. 5 lines 15-19 and US 6,290,930, col. 3 lines 40-45.

The formulations of the present invention contain neither a propellant nor a lipophilic counterion. There is no component in the formulations of Applicant's invention, which is the functional equivalent of either a propellant or a lipophilic counterion. Although Examiner appears to equate a lipophilic counterion with a derivatized carbohydrate, there is nothing in the prior art to suggest such equivalence. The purpose of the lipophilic counterion taught by Adjei is to improve the equilibrium solubility of the LHRH analog in the co-solvent systems described by Adjei. Furthermore, Applicant's claimed composition does not contain a derivatized carbohydrate.

Claims 1, 5, 6 and 14 are rejected under 35 USC 102(b) as being anticipated by Ban et al. (HU 62473) on the grounds that:

> Ban teaches an aerosol formulation comprising organic solvent (ethanol), an oestrogenic hormone (protein) suspended in ethanol or in polypropylene glycol and 1-amyl-nitrate (derivatized carbohydrate).

The Ban et al. abstract describes a biocomposition useful to increase erogenous zone sensitivity. The composition may be an ointment or a spray. Dorlands Medical dictionary describes the term "erogenous zone" as follows:

> "a portion of the body stimulation of which produces erotic excitement; such as the genitals, urethra, lips, anus, and breasts." Dorland's Illustrated Medical Dictionary, 25th Ed., 1974, W.B. Saunders, Philadelphia, p. 1745.

Ban discloses a formulation containing the following components:

%w/w	Active Ingredients
0.01-1.0	Isoamylnitrite*
0.01-0.6	Vitamin E or A
0-0.5	Androgenic or Estrogenic Hormones

It is assumed that the compound referred as "isoamylnitrite" is actually isoamyl nitrate; amyl nitrite or isoamyl nitrite is a flammable liquid that forms an explosive mixture with air or oxygen and is incompatible with alcohol. Merck Index 11th Ed., 1989, p. 5013, Merck & Co., Inc., Rahway, N.J., USA. Amyl nitrate is a coronary vasodilator, which is chemically related to nitroglycerin. It is frequently abused as an aphrodisiac.

The components in the formulations of Ban are dissolved, emulsified or suspended in various vehicles, e.g., dilute aqueous ethanol, propylene glycol, polyethylene glycol, polypropylene glycol base or an oil soluble ointment base.

The compositions of Ban contain neither a protein nor a derivatized carbohydrate. Estrogen and testosterone can act as hormones but chemically they are steroids not proteins or peptides. Amyl nitrate is neither a carbohydrate nor a protein but a small organic molecule. Although Examiner is incorrect in characterizing amylnitrate as a "derivatized carbohydrate", it is irrelevant because Applicant's claimed composition does not contain a derivatized carbohydrate.

Invalidity for anticipation requires that all of the elements and limitations of the claim be found within a single prior art reference. There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Found. v. Genentech Inc.*, 18 USPQ 2d 1001, 1010 (Fed. Cir. 1991). Neither the Adjei reference nor the Ban reference teaches a composition containing a protein as the active drug substance suspended in an ethanol carrier liquid. Accordingly, neither of these references anticipates Applicant's invention as described by any of the claims presently in the above-identified application.

B. Rejection Under 35 USC §103(a)

Claims 2 – 4, 10, 13 and15 stand rejected under 35 USC 103(a) as being unpatentable over Adjei on the grounds that:

> Adjei recites all that is in Claims 2 – 4, 10, 13 and15 except for the aerosol comprising the instant amounts of ingredients and instant particle size.

Contrary to Examiner's assertion, Adjei does not recite "all" that is in Applicants claims but rather "more". The composition of Adjei is required to contain a propellant and a lipophilic counterion. There is no teaching or suggestion in Adjei that would lead one skilled in the art to omit two essential components i.e., the lipophilic counterion and propellant to produce the composition of Applicant's claimed invention.

Adjei teaches that LHRH analogs are practically insoluble in fluorocarbons and that in mixtures of ethyl alcohol and fluorocarbons, the solubility of leuprolide approaches 3 mg/ml, which is not satisfactory due to dose requirements. In mixtures of fluorocarbons, ethyl alcohol and water, experimental results showed equilibrium solubility of leuprolide to approach 5 mg/ml which was still unacceptable. At high concentrations of ethyl alcohol, a gel-like mass formed resulting in a colloidal dispersion that did not clear at room temperature for up to one month. At water concentrations of 10% or greater, a complete phase separation occurred making a homogeneous formulation impractical and rendering aerosolization impractical.

The problem facing Adjei was getting enough active (leuprolide) in solution without having the composition gel or undergo phase separation. Adjei solved these problems by the addition of the lipophilic counterion to the solvent system.

There is nothing in Adjei, which would point the skilled artisan to the invention claimed herein. The problem solved by Applicant is the preservation of bioactivity over time of a protein or peptide suspended in ethanol. Solubility of the protein in the solvent system is not an issue because the biologically active protein exists as a solid suspended in the continuous phase liquid.

The claimed invention is directed to a formulation or composition, which is a combination of elements, i.e., a combination of ingredients or compounds. Applicants do not claim to have invented one or more new elements (components) but rather claim a new combination of elements. To support the conclusion that the claimed combination is directed to obvious subject matter, either Adjei must expressly or impliedly suggest the claimed combination or Examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to be obvious in light of the teachings of the reference. *Ex parte Clapp*, 227 USPQ 972, 973 (B.P.A.I. 1985). Based on the arguments presented above it is respectfully asserted that the Adjei reference fails to teach or suggest the formulation of the present invention and that Examiner has failed to present any evidence to the contrary.

The Ban reference describes a conventional ointment or sprayable liquid containing as the active ingredients a mixture of androgens or estrogens, Vitamin E and A and isoamylnitrate. The ointment or spray is useful to stimulate erogenous zones and thus, would be applied topically. There is absolutely no suggestion in the Ban reference that either the ointment or the spray is suitable for inhalation. The compositions of Ban do not contain a protein or peptide suspended in ethanol. There is nothing in Ban that would motivate the skilled artisan to modify the compositions of Ban to the extent necessary to arrive at the compositions of the present invention.

Based on the arguments and amendments made herein, it is respectfully asserted that Claims 1-5, 7, and 34-35 directed to a stable formulation of a biologically active protein are in condition for allowance. Examiner is respectfully requested to withdraw the rejections under 35 USC §102(b), and 35 USC §103(a) and to issue a Notice of Allowance.

Respectfully submitted,

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